



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :	A1	(11) International Publication Number: WO 99/38551
A61M 5/142, 5/14		(43) International Publication Date: 5 August 1999 (05.08.99)

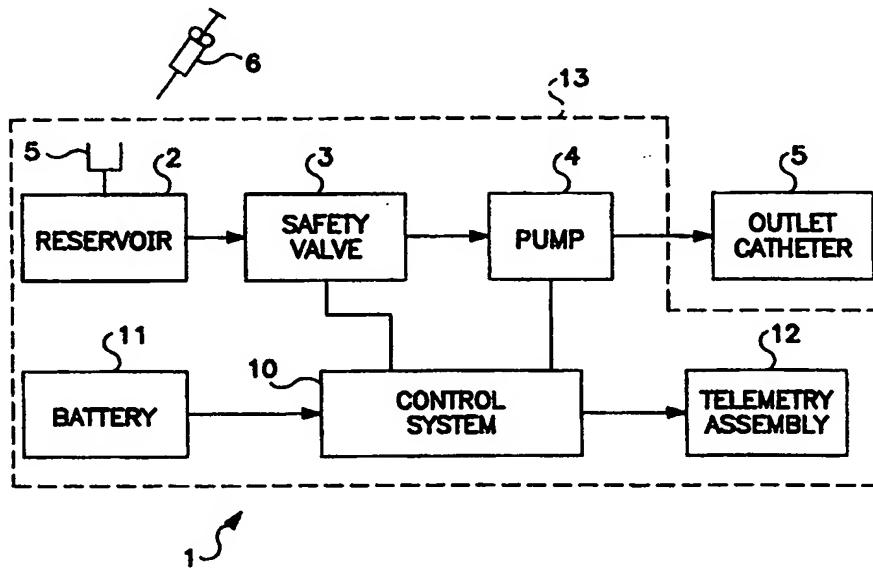
(21) International Application Number: PCT/US99/02083	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 1 February 1999 (01.02.99)	
(30) Priority Data: 09/017,195 2 February 1998 (02.02.98) US	
(71) Applicant: MEDTRONIC, INC. [US/US]; 7000 Central Avenue N.E., Minneapolis, MN 55432 (US).	
(72) Inventors: WEIJAND, Koen, J.; Moerbeekstraat 73, NL-3235 EG Rockanje (NL). HALLER, Markus; 24, route de Burtigny, CH-1268 Begnins (CH).	
(74) Agents: JARO, Michael, J. et al.; Medtronic, Inc., MS 301, 7000 Central Avenue N.E., Minneapolis, MN 55432 (US).	

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: IMPLANTABLE DRUG INFUSION DEVICE HAVING A SAFETY VALVE



(57) Abstract

An implantable drug infusion device (1) which features a safety valve (3). The safety valve (3) is normally in the closed state and only opens upon electrical activation. The valve (3) is designed so as to be constructed in an extremely small size and further to be made of corrosion resistant materials. The valve may be used in either a passive or an active drug infusion system. Also disclosed is an efficient circuit to drive, i.e. open and close, the safety valve. Further disclosed is a timing scheme for opening and closing the safety valve for use in an active drug infusion device.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

IMPLANTABLE DRUG INFUSION DEVICE
HAVING A SAFETY VALVE

RELATED APPLICATIONS

5 This application is related to one or more of the following each of which are filed on this same day each incorporated herein by reference and each assigned to the assignee of the present application:

- United States patent application entitled "System For Locating Implantable Medical Device" of Markus Haller and Koen Weijand (Our File: P-7521);

10 - United States patent application entitled "Implantable Drug Infusion Device Having A Flow Regulator" of Markus Haller, Phillip Renaud and Christian Amacker (Our File: P-7322 (Including P-7353)); and

- United States patent application entitled "Implantable Drug Infusion Device Having An Improved Valve" of Markus Haller, T. S. J. Lammerink and Niels Olij (Our File: P-7356).

FIELD OF THE INVENTION

The present invention relates to the field of implantable drug infusion devices and more particularly to an implantable drug infusion device having a safety valve.

20 BACKGROUND OF THE INVENTION

Implantable drug infusion devices are used to provide patients with a constant and long term dosage or infusion of a drug or any other therapeutic agent. Essentially such device may be categorized as either active or passive.

25 Active drug or programmable infusion devices feature a pump or a metering system to deliver the drug into the patient's system. An example of such an active drug infusion device currently available is the Medtronic SynchroMed programmable pump. Such pumps typically include a drug reservoir, a peristaltic pump to pump out the drug from the reservoir, and a catheter port to transport the pumped out drug from the reservoir via the pump to a patient's anatomy. Such devices also typically include

a battery to power the pump as well as an electronic module to control the flow rate of the pump. The Medtronic SynchroMed pump further includes an antenna to permit the remote programming of the pump.

Passive drug infusion devices, in contrast, do not feature a pump, but rather rely upon a pressurized drug reservoir to deliver the drug. Thus such devices tend to be both smaller as well as cheaper as compared to active devices. An example of such a device includes the Medtronic IsoMed™. This device delivers the drug into the patient through the force provided by a pressurized reservoir. In particular, this reservoir is pressurized with a drug to between 20-40 psi through a syringe capable of delivering the fluid between 35-55 psi.

Regardless of whether the device is an active or passive drug infusion device, the overriding concern for all drug infusion devices is to ensure patient safety. This includes, among many other things, that only the exact intended amount of drug is delivered to the patient. Thus, one drawback to active devices which feature pumps that are not normally closed, such as those seen in U.S. Patent Nos. 5,277,556; 5,224,843 and 5,219,278, is that if the device malfunctions or changes occur in the fluid pathway, then more drug than intended may reach the patient. Similar risks are inherent in passive devices which, should the flow regulator fail or the pressure reservoir be over pressurized, may lead to more drug than intended to reach the patient.

Thus there is a need for a drug infusion system which features a safety valve which will provide an additional margin of safety to the patient.

SUMMARY OF THE INVENTION

The present invention provides an implantable drug infusion device which features a safety valve. The safety valve is normally in the closed state and only opens upon electrical activation. The valve is designed so as to be constructed in an extremely small size and further to be made of corrosion resistant materials. The valve may be used in either a passive or an active drug infusion system. Also disclosed is an

efficient circuit to drive, open and close, the safety valve. Further disclosed is a timing scheme for opening and closing the safety valve for use in an active device.

BRIEF DESCRIPTION OF THE DRAWINGS

5 FIG. 1 is a block diagram of the present invention.

FIG. 2A is a side view of the safety valve used in the present invention.

10 FIG. 2B shows a safety valve in an open position and thereby permitting fluid to flow.

FIGS. 3A and 3B disclose an alternative embodiment of the safety valve used in the present invention.

15 FIG. 4 is a schematic diagram of a driver circuit used to control the piezo membrane of the embodiment shown in FIGS. 2A and 2B which recollects the stored energy on the piezo when the voltage on the piezo is turned to zero.

FIG. 5 is a timing diagram of the operation of the driver circuit shown in FIG. 4.

FIG. 6 depicts an alternative driver circuit for the piezo membrane of FIG. 2.

FIG. 7 is a timing diagram of the circuit shown in FIG. 6.

The FIGS. are not necessarily to scale.

DETAILED DESCRIPTION OF THE DRAWINGS

20 FIG. 1 is a block diagram of the present invention. As seen, such a system 1 comprises a reservoir 2, safety valve 3, pump 4, electronic controls 10, battery 11, telemetry assembly 12 and outlet catheter 5. Outlet catheter may be of any model desired and suited to the patient's requirements. Safety valve 3 is coupled to the reservoir and also to pump 4. Pump may be of any suitable design, including a roller-type pump as found in the SynchroMed™ or a micro-machined pump, for example. Pump 4 is coupled, in turn to outlet catheter 5, such that fluid form reservoir 2 may be pumped through safety valve and out to outlet catheter. Pump is controlled by electronic controls 10. These controls include, among other devices, an efficient circuit to drive the membranes used in safety valve 3. The device may be refilled

through injection port 5 through the use of a needle 6 as is well known. This refill procedure may be further enhanced through the use of the system as described in the above referenced United States patent application entitled "System For Locating Implantable Medical Device" of Markus Haller and Koen Weijand (Our File: P-7521). Surrounding all components of the implantable pump other than the outlet catheter is a hermetic closure 13 as is well known in the art. The device may further feature, if desired, a flow regulator, such as that shown in the above referenced United States patent application entitled "Implantable Drug Infusion Device Having A Flow Regulator" of Markus Haller, Phillip Renaud and Christian Amacker (Our File: P-7322 (Including P-7353)).

FIG. 2A is a side view of the safety valve used in the present invention. As seen, safety valve 3 is constructed with a first membrane 20 in tension and a second membrane 21. Membranes are preferably constructed from piezo electric material such as silicon, but may also be constructed using other types of materials, including piezo resistive or piezo capacitive. As seen, membrane 20 includes seal 22. Seal 22 may be constructed of any desired material, such as for example, silicon or polyimide. Membrane 20 is disposed from shoulders 23 and 24 and is typically biased in a downward or closed manner, i.e., such that seal 22 engages the tip surface of substrate 25, thus occluding passage 30. Mounted to the bottom surface of substrate is membrane 31. As seen, membrane 31 is mated to membrane 21. Membrane 31 is constructed of silicon. As further seen, membrane 31 further features a nipple portion 32 having an end cap portion 33. End cap engages against seal 22 and assists in occluding fluid passage 30. Membrane 31 is mounted so as to be biased in an upward direction, i.e., such that end cap 33 is disposed against seal 22.

FIG. 2B shows a safety valve in an open position and thereby permitting fluid to flow. As discussed above, safety valve is controlled by piezo electric membranes. As seen in this view, the piezo electric membrane 21 has been energized such that the bias is removed and the membrane bends downwardly, away from seal 22. In this manner the membrane removes the blockage to passageway 30 and thus permits fluid to flow from the area above substrate 25 through passageway 30 and thus out

passageway 35. Of course, because membrane 21 is typically biased in the upwards direction, upon the removal of energy to membrane 21, the membrane moves back into the position such that end cap 33 engages against seal 22.

FIGS. 3A and 3B disclose an alternative embodiment of the safety valve used in the present invention. In particular, this embodiment features shape memory alloy membranes as opposed to piezo electric membranes disclosed above. This embodiment features a superior membrane 40 and an inferior membrane 41. Membrane 40 is biased in an upward direction while membrane 41 is biased in a downward direction. The respective biasing strengths of these membranes controls membrane 40 to normally close the valve when no energy is provided to membrane 41. Upon energizing the membrane 41, however, the shape memory alloy undergoes a reorganization of the crystalline structure. As constructed, this removes the bias to membrane 41. Membrane 40 will, in turn, overcome the bias provided by membrane 41 and thus move the seal assembly 42 upwardly and away from seal footing 43 mounted on substrate 44 thereby creating a fluid passage from cavity 45 to passageway 50. As seen, membrane 40 is mounted across shoulder elements 50 and 51 and includes center portion 52. Shoulder and center portion are preferably constructed of glass. As further seen, membrane 41 is disposed on the downward surface of shoulder and center portion and further mounted to bases 53 and 54. Bases as well as seal assembly 42 are also constructed from glass. This entire assembly is further mounted to substrate 44 through contacts 60 and 61. Contacts 60 and 61 are preferably constructed from silicone. Substrate 44 is preferably constructed of glass while footing 43 is constructed of silicone. Membranes are preferably constructed from Nitinol, although other shape memory alloys may also be used. Moreover, the areas of substrate and membranes in contact with any drug or fluid are further preferably coated with diamond or diamond-like carbon so as to inhibit any interactions between the drug or fluid and the materials. Such coatings may be selected according to the particular drug or fluid to be infused, and may include also tantalum or titanium, for example.

Essentially, the operation of this embodiment may be seen in compared FIGS. 3A and 3B. At rest, or when no energy is provided to membranes, the particular bias to membranes causes seal assembly 42 to snugly engage against footing 43. Once energy is provided to the membranes, the energy or electric current causes the material to heat up and thereby ending the phased transformation, i.e., the crystalline structure is reorganized. Thus seal assembly 42 is caused to disengage against footing 43 and thereby opens a fluid pathway from cavity 45 into passageway 50. Of course, although in this embodiment a double membrane design is shown, other embodiments may feature a single, biased membrane as well as three or more membranes, depending upon the exact fluid pathway required.

On difficulty with all battery powered implantable devices is that they must operate with as little energy drain as possible. One problem associated with past usage of piezo membranes is that past driver circuits typically dissipated the charge built up after a voltage was applied across the membrane. This, of course, wasted energy, and particularly such built-up charge. Another feature of the present invention is the use of a driver circuit which minimizes the energy used. In particular, the present invention further features a driver circuit which recollects the stored energy on the piezo when the voltage on the piezo is turned to zero.

FIG. 4 is a schematic diagram of a driver circuit used to control the piezo membrane of the embodiment shown in FIGS. 2A and 2B which recollects the stored energy on the piezo when the voltage on the piezo is turned to zero. FIG. 5 is a timing diagram of the operation of the driver circuit shown in FIG. 4. Each of these FIGS. will now be described together. As seen, the circuit consists of a 3V power supply, four N-MOS switches with low ohms resistance, 1 P-MOS switch, a storage capacitor and inductor and a piezo membrane. M1 and M2 are high voltage devices while M3-M5 are low voltage devices. At its initial condition, all switches are closed except M5. In step 1 (with reference also to FIG. 5,) M3 and M4 are opened and M5 is closed to thereby charge capacitor C2 through inductor L1. In step 2, M2 is opened and M3 is closed to thereby connecting inductor L1 to piezo. The current in L1 is maintained and a voltage is developed on the drain of M2, as best illustrated by

line 99 in FIG. 5, and a voltage is thereby developed across piezo. Once voltage in piezo (or L1) reaches a maximum level step 3 begins. As seen in this step M1 is opened and M2 is closed thereby shorting L1 and maintaining the charge on piezo. Charge actuates the piezo and may be maintained on the piezo for as long as actuation is desired. In steps 4, 5 and 6 the process is reversed. In step 4, M2 is opened, M1 is closed thereby discharging the piezo voltage through the inductor. In step 5 M3 is opened and M2 is closed and the current through L1 is flowed through C2 thereby discharging C2. Finally in step 6, M5 is opened and M3 and M4 are closed, thereby returning to initial conditions. In such a manner the piezo may be driven through a minimal amount of energy. As seen the amount of energy delivered to piezo is determined by the amount of energy delivered to L1, which may be determined by the time which elapses between step 1 and step 2. Of course, if C1 is not completely charged full, then operation is slightly changed, and in step 2 M5 opened, M4 opened and M3 closed. Thereafter the operation remains as described although in step 5 M5 is closed. Additional functionality to monitor voltages or current or both and determine the proper timing for closing the switches is not shown, but would be performed in block 10 of FIG. 1, labeled control system.

FIG. 6 depicts an alternative driver circuit for the piezo membrane of FIG. 2. FIG. 7 is a timing diagram of the circuit shown in FIG. 6. Each of these FIGS. will now be described together. As seen, this circuit consists of a 3V power supply, a storage capacitor - C1, a piezo model capacitor - C2, an inductor - L1, and four N-MOS switches - M1-M4. The pulses S1-S3 are 10V square wave pulses created by the pulse generation circuit.

The first step in creating the piezo drive pulse is to charge the storage capacitor, C1, to the voltage level of the power supply by closing switches M1 and M3/M4. After C1 is fully charged to the supply voltage, the inductor, L1, is charged with current by discharging the stored energy in C1. This is done by simultaneously opening M1 while closing M2 and keeping M3/M4 closed. Then M2 is reopened while M3/M4 remains closed to charge the piezo, C2, with the stored current. The voltage on C2 rises to 150V and all switches are opened while the pulse remains high.

After the high pulse on the piezo is finished, M3/M4 is closed to drain the energy from the piezo into the inductor L1. After the piezo is drained switch M2 is closed, while M3/M4 remains closed, to charge C2 with the energy stored in the inductor L1. The cycle begins again with another rising edge on M1. The following timing diagram displays the timing sequence for closing of switches M1, M2, and M3/M4 where time units are in seconds.

Although a specific embodiment of the invention has been disclosed, this is done for purposes of illustration and is not intended to be limiting with regard to the scope of the invention. It is contemplated various substitutions, alterations and/or modifications may be made to the disclosed embodiment without departing from the spirit and scope of the invention. Such modifications may include substituting elements or components which perform substantially the same function in substantially the same way to achieve substantially the same result for those described herein.

What is claimed is:

1. An implantable drug infusion device comprising:
 - a hermetic enclosure;
 - 5 a fluid reservoir positioned within the hermetic enclosure, the fluid reservoir having means for maintaining the fluid therein within a first pressure and a second pressure;
 - means for delivering a fluid into a patient's body;
 - 10 a pump, the pump communicating with the reservoir and the means for delivering a fluid into a patient's body, the pump causing fluid to move from the reservoir into the means for delivering a fluid into a patient's body; and
 - 15 a safety valve moveable between a first non-energized position, in which the movement of fluid from the reservoir into the means for delivering a fluid into a patient's body is prevented, to a second energized position, in which the movement of fluid from the reservoir into the means for delivering a fluid into a patient's body is permitted
2. An implantable drug infusion device according to claim 1 further comprising the safety valve is in the normally first non-energized position
- 20 3. An implantable drug infusion device according to claim 1 further comprising a the surfaces of the valve in contact with the fluid have a coating of diamond or diamond-like carbon whereby interactions between the fluid and the materials are inhibited.
- 25 4. An implantable drug infusion device according to claim 1 further comprising the safety valve further comprises a first membrane in tension and a second membrane, the first and second membranes disposed in parallel, the first membrane has a seal, such that the seal obstructs the movement of fluid from the reservoir into

the means for delivering a fluid into a patient's body is prevented when the valve is in the first non-energized position.

5. An implantable drug infusion device according to claim 4 further comprising the membranes are constructed from piezo electric material.

6. An implantable drug infusion device according to claim 5 further comprising the membranes are constructed from silicon.

10 7. An implantable drug infusion device according to claim 1 further comprising a superior membrane and an inferior membrane, superior membrane is biased in a first direction while inferior membrane biased in a second direction.

15 8. An implantable drug infusion device according to claim 7 further comprising first and second membranes are constructed from a shape memory alloy.

9. An implantable drug infusion device according to claim 8 further comprising the superior and inferior membranes mounted are across shoulder element and featuring a center portion therebetween.

20 10. An implantable drug infusion device according to claim 9 further comprising shoulder and center portion are constructed of glass.

25 11. An implantable drug infusion device according to claim 10 further comprising the inferior membrane disposed on a first surface of shoulder.

12. An implantable drug infusion device according to claim 1 further comprising means for delivering electrical energy to the membranes and thereby energize the valve.

13. An implantable drug infusion device according to claim 12 further comprising means for recollecting the energy delivered to the membranes when the valve is moved from the second energized position to the first non-energized position.

5 14. An implantable drug infusion device according to claim 13 further comprising the membranes are constructed of a piezo electric material.

15. An implantable drug infusion device according to claim 13 further comprising the membranes are constructed of a shape memory alloy.

10 16. An implantable drug infusion device comprising:
a hermetic enclosure;
a fluid reservoir positioned within the hermetic enclosure, the fluid reservoir having means for maintaining the fluid therein within a first pressure and a second pressure the pressure causing fluid to move from the reservoir into the means for delivering a fluid into a patient's body;
means for delivering a fluid into a patient's body; and
a safety valve moveable between a first non-energized position, in which the movement of fluid from the reservoir into the means for delivering a fluid into a
15 patient's body is prevented, to a second energized position, in which the movement of fluid from the reservoir into the means for delivering a fluid into a patient's body is permitted
20

25 17. An implantable drug infusion device according to claim 16 further comprising the safety valve is in the normally first non-energized position.

30 18. An implantable drug infusion device according to claim 16 further comprising a the surfaces of the valve in contact with the fluid have a coating of diamond or diamond-like carbon whereby interactions between the fluid and the materials are inhibited.

19. An implantable drug infusion device according to claim 16 further comprising the safety valve further comprises a first membrane in tension and a second membrane, the first and second membranes disposed in parallel, the first membrane has a seal, such that the seal obstructs the movement of fluid from the reservoir into the means for delivering a fluid into a patient's body is prevented when the valve is in the first non-energized position.

5

20. An implantable drug infusion device according to claim 19 further comprising the membranes are constructed from piezo electric material.

10

21. An implantable drug infusion device according to claim 20 further comprising the membranes are constructed from silicon.

15

22. An implantable drug infusion device according to claim 16 further comprising a superior membrane and an inferior membrane, superior membrane is biased in a first direction while inferior membrane biased in a second direction.

20

23. An implantable drug infusion device according to claim 22 further comprising first and second membranes are constructed from a shape memory alloy.

24. An implantable drug infusion device according to claim 23 further comprising the superior and inferior membranes mounted are across shoulder element and featuring a center portion therebetween.

25

25. An implantable drug infusion device according to claim 24 further comprising shoulder and center portion are constructed of glass.

30

26. An implantable drug infusion device according to claim 25 further comprising the inferior membrane disposed on a first surface of shoulder.

27. An implantable drug infusion device according to claim 16 further comprising means for delivering electrical energy to the valve and thereby energize the valve causing it to move from the first position to the second position.

5

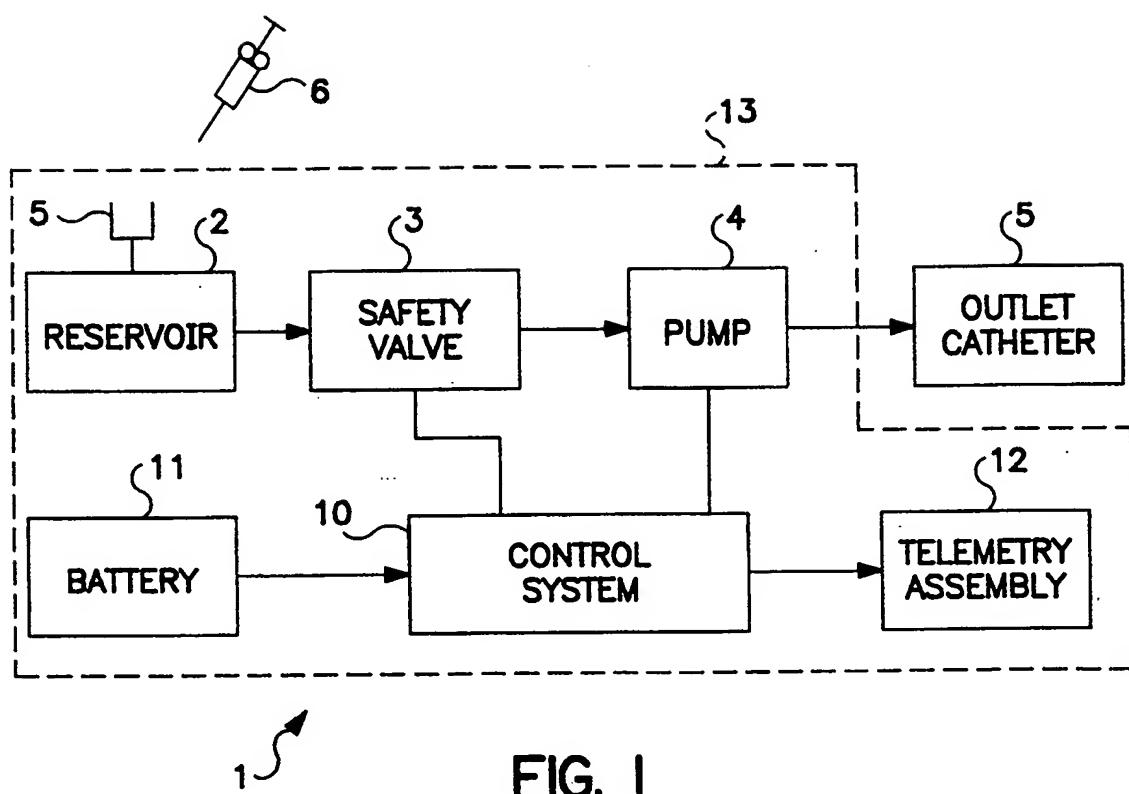
28. An implantable drug infusion device according to claim 27 further comprising means for recollecting the energy delivered to the valve when the valve is moved from the second energized position to the first non-energized position.

10

29. An implantable drug infusion device according to claim 28 further comprising the valve comprises a piezo electric material.

30. An implantable drug infusion device according to claim 28 further comprising the membranes comprises of a shape memory alloy.

15



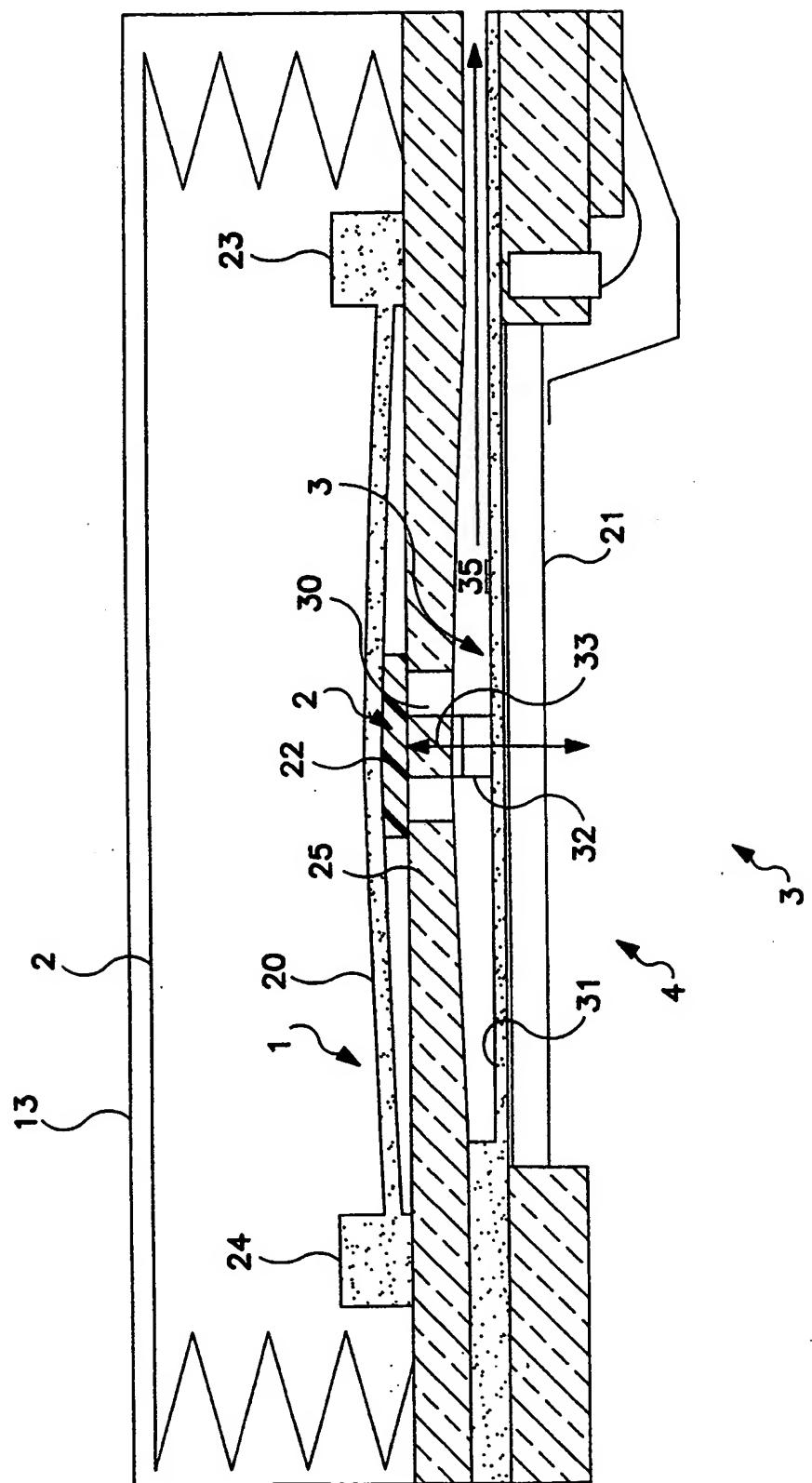


FIG. 2A

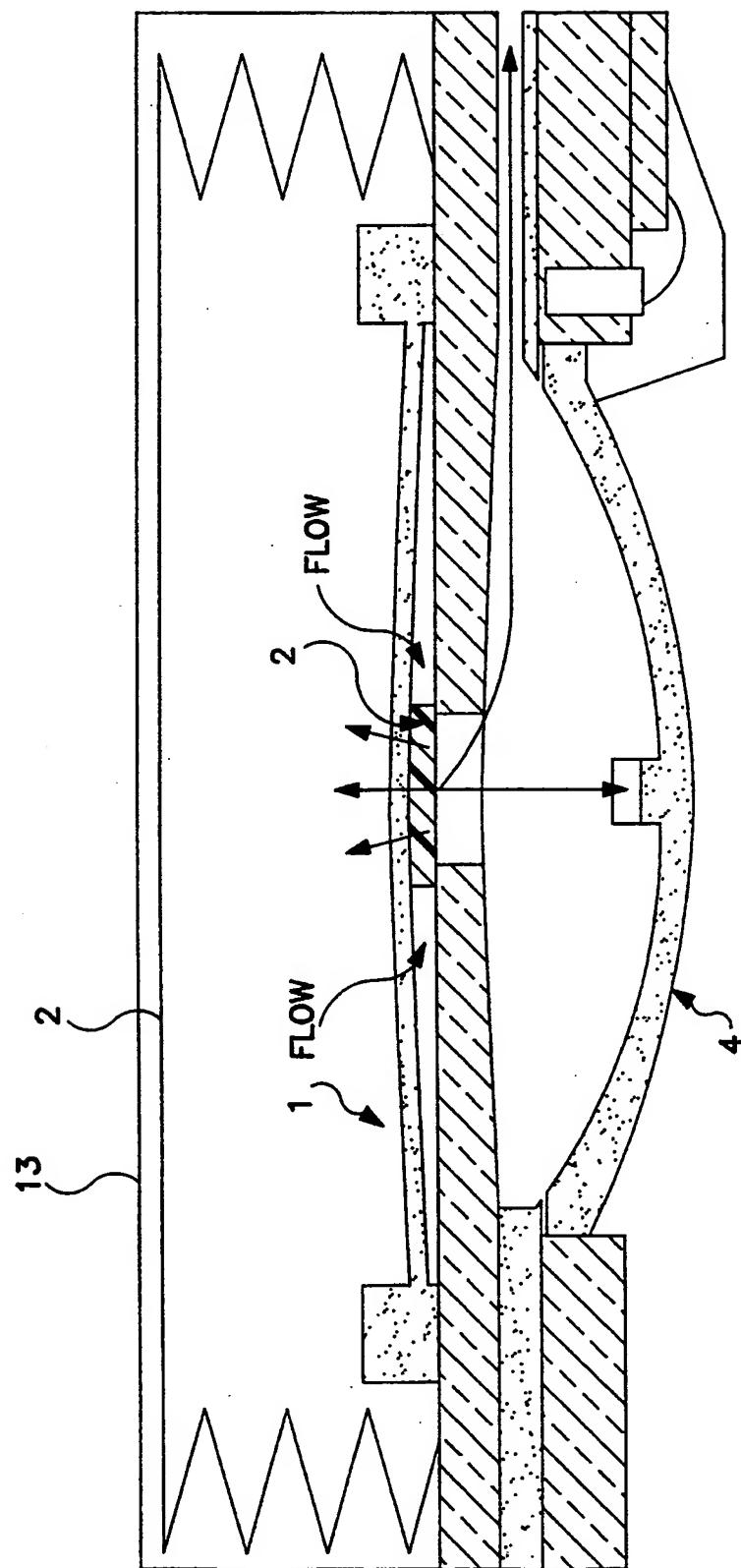


FIG. 2B

4 / 8

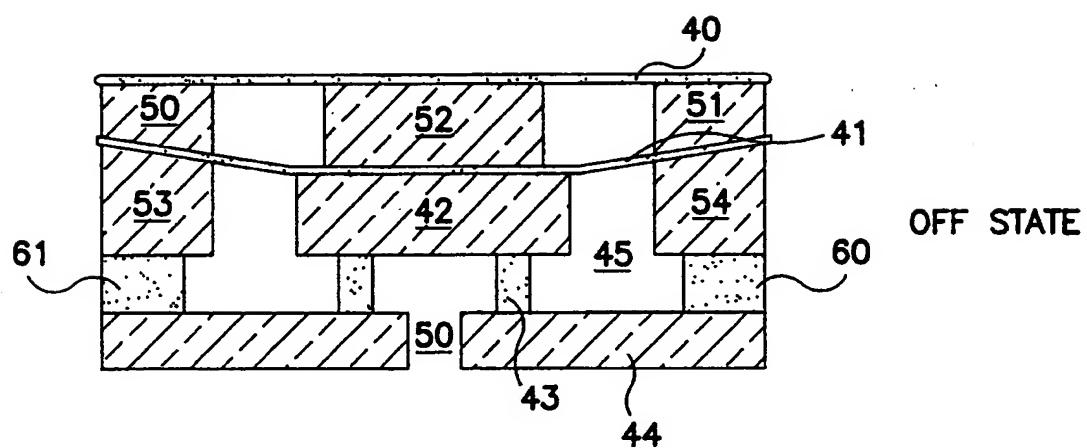


FIG. 3A

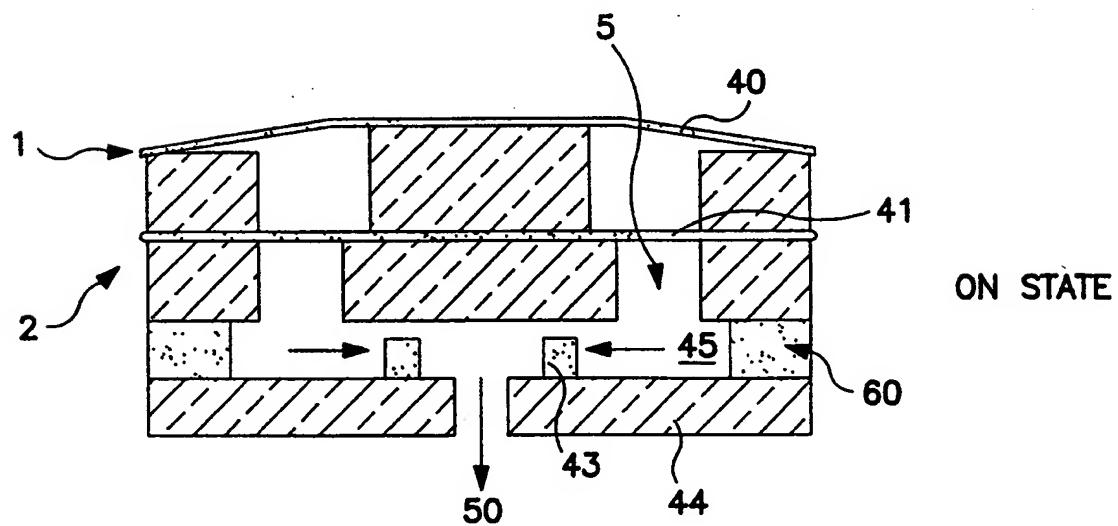


FIG. 3B

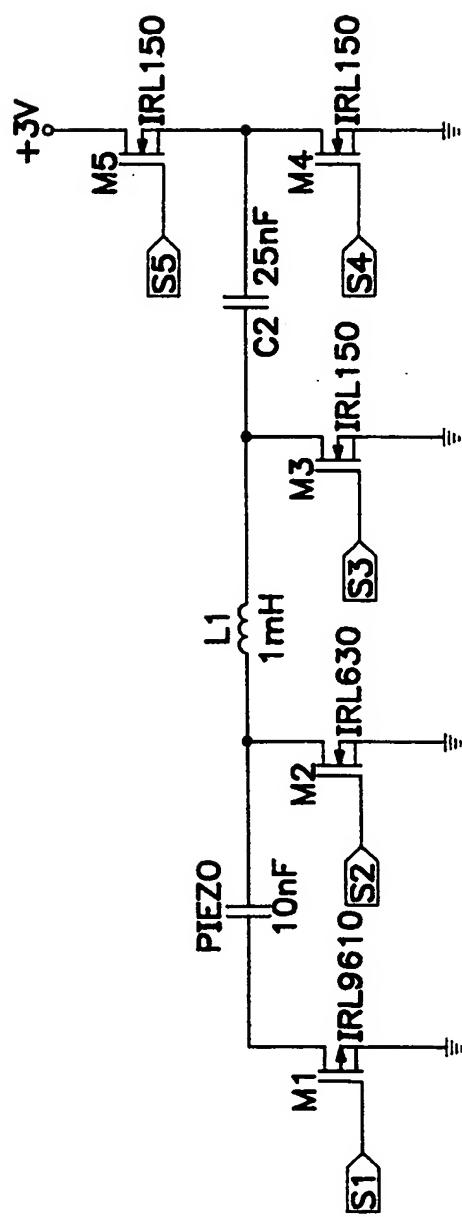


FIG. 4

6 / 8

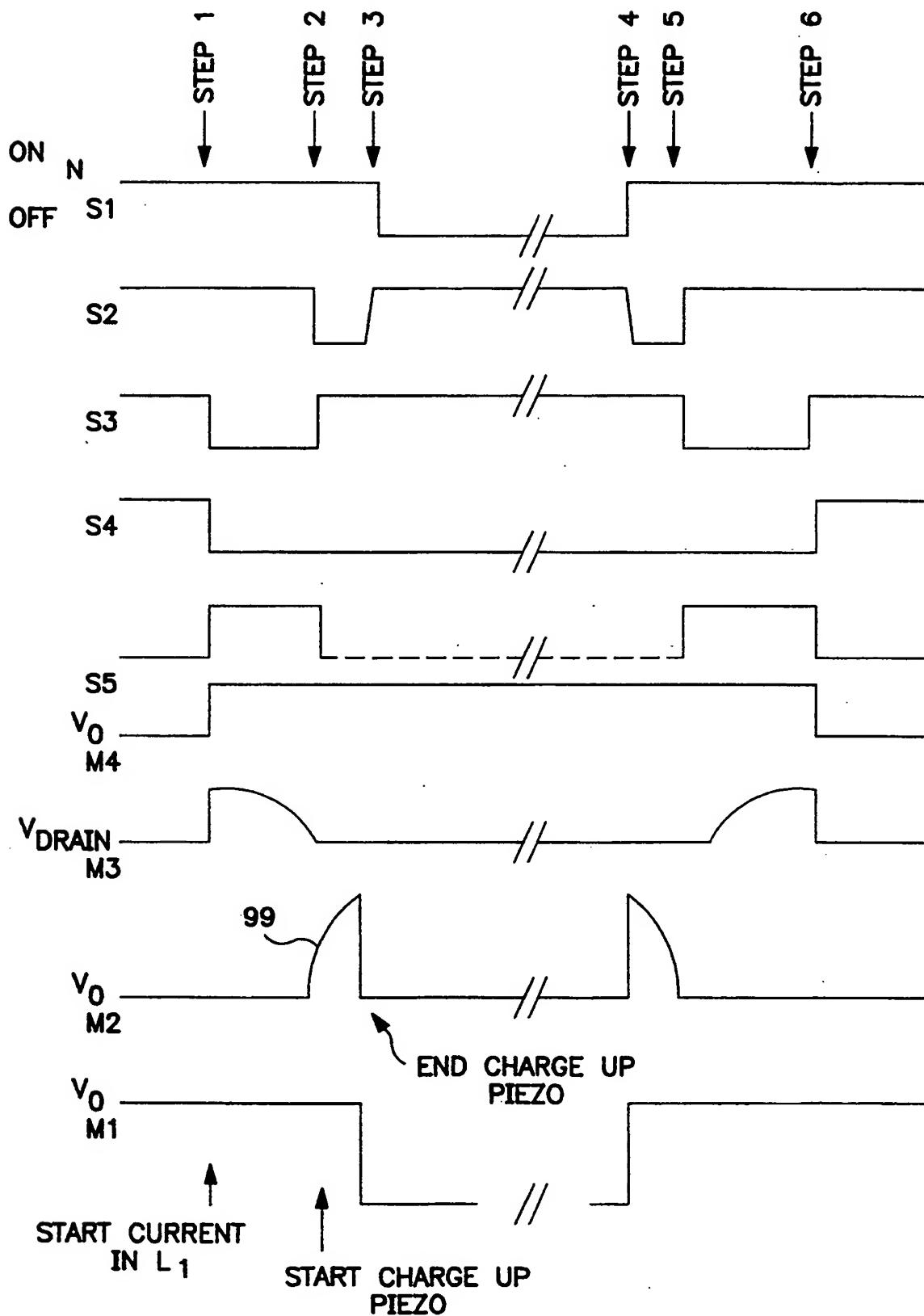


FIG. 5

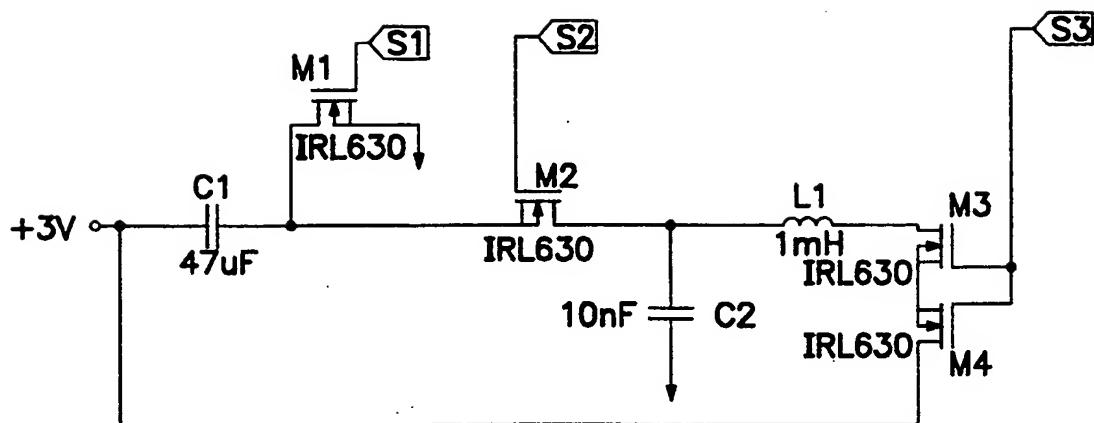


FIG. 6

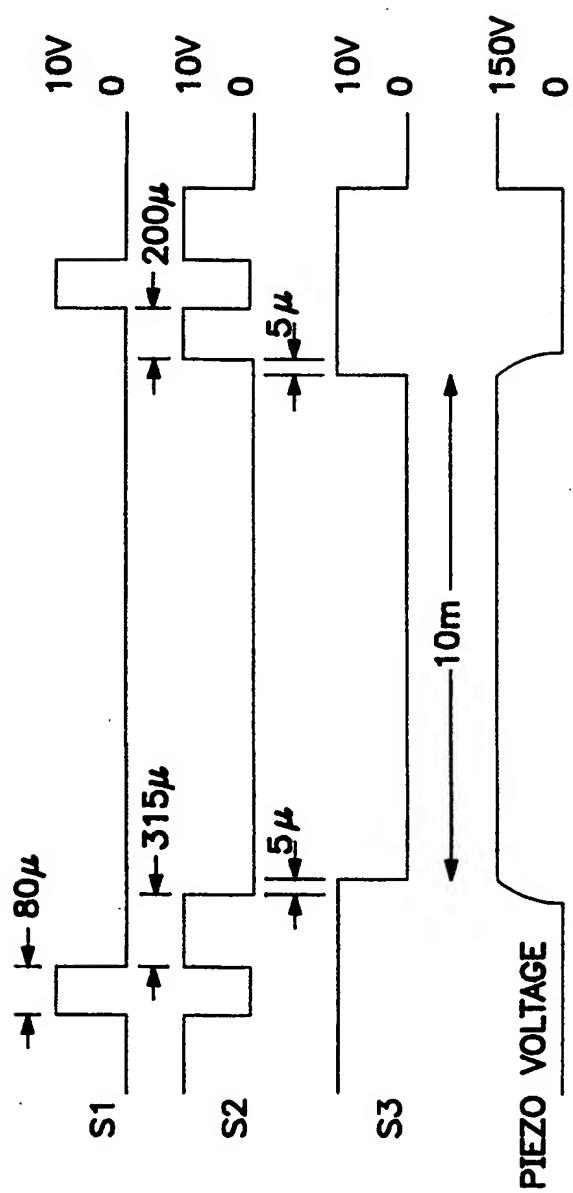


FIG. 7

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/02083

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M5/142 A61M5/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M A61F F04B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 387 439 A (SHILEY INFUSAD INC) 19 September 1990	1,2,12, 16,17,27
A	see column 4, line 54 - column 8, line 30; figures 1,2A,3 ---	18
X	EP 0 450 186 A (LAGUETTE) 9 October 1991	1,2
A	see column 8, line 15 - column 12, line 45; figures 1,3,5 ---	9,10,17
A	US 5 277 556 A (VAN LINTEL) 11 January 1994	2,4-6, 10-12, 14,17, 19-21, 24,25, 27,29
	see abstract; figure 1 ---	
A	EP 0 039 124 A (INFUSAID) 4 November 1981 -----	

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

21 June 1999

Date of mailing of the international search report

29/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Germano, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/02083

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 387439	A	19-09-1990	US 4838887 A		13-06-1989
			AU 603035 A		01-11-1990
EP 450186	A	09-10-1991	US 5152753 A		06-10-1992
			AT 118360 T		15-03-1995
			CA 2030767 A,C		03-10-1991
			DE 69017004 D		23-03-1995
			DE 69017004 T		08-06-1995
			JP 7047136 A		21-02-1995
			JP 8024720 B		13-03-1996
			US 5085644 A		04-02-1992
US 5277556	A	11-01-1994	CH 683634 A		15-04-1994
			CH 684209 A		29-07-1994
			AT 119241 T		15-03-1995
			AU 642285 B		14-10-1993
			AU 8184191 A		04-02-1992
			CA 2065735 A		11-01-1992
			DE 69107813 D		06-04-1995
			DE 69107813 T		09-11-1995
			WO 9201160 A		23-01-1992
			EP 0491026 A		24-06-1992
			ES 2069896 T		16-05-1995
			JP 2824975 B		18-11-1998
			JP 5502083 T		15-04-1993
EP 0039124	A	04-11-1981	CA 1154345 A		27-09-1983
			DK 104581 A,B,		08-09-1981
			JP 56136562 A		24-10-1981